

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



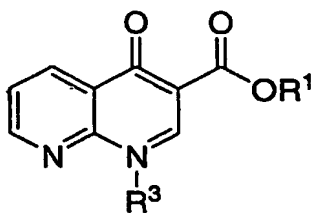
(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/048377 A3

- (51) International Patent Classification⁷: **C07D 471/04**
- (21) International Application Number:
PCT/US2003/036806
- (22) International Filing Date:
18 November 2003 (18.11.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/428,315 22 November 2002 (22.11.2002) US
60/472,655 22 May 2003 (22.05.2003) US
- (71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ALBANEZE-WALKER, Jennifer** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MURRY, Jerry, Anthony** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SOHEILI, Arash** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SPRINGFIELD, Shawn, A.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:
2 September 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF PREPARING INHIBITORS OF PHOSPHODIESTERASE-4



(V)

(57) Abstract: In one aspect, the present invention is directed to a one pot method of preparing intermediates of Formula (V), which are useful in making inhibitors of phosphodiesterase-4. The present invention is also directed to a method of preparing phosphodiesterase inhibitors comprising the Formula (IX, IXa).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/36806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 25 50 111 A (RHONE POULENC IND) 13 May 1976 (1976-05-13) examples 2,4,5,9,10,14-18,23,24,27-29,36,39	16-18
A	"Improved synthesis of unsymmetrical heteroaromatic 1,2-diketones and the synthesis of carbazole ring substituted tetraaryl cyclopentadienenones" J. ORG. CHEM., vol. 64, no. 16, 1999, pages 6102-6105, XP002274463 scheme 1; page 6104, left column, preparation of compound 4 --- -/--	1-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 June 2004

Date of mailing of the international search report

01 07. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schmid, A

INTERNATIONAL SEARCH REPORT

International Application No

P US 03/36806

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WOLFE J P: "Highly active palladium catalysts for Suzuki coupling reactions" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 121, no. 41, 20 October 1999 (1999-10-20), pages 9550-9561, XP002132767 ISSN: 0002-7863 cited in the application the whole document</p>	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/36806

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15

Method for the preparation of the compounds of formula IX and IXa

2. Claims: 16-18

method of purifying a compounds of formula IX and IXa

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1(partly)

The 1st claim appears to be directed the preparation of compounds IX and IXa. However, in the course of this claim it becomes clear that compounds according to formulae VIII and VIIla are prepared. Therefore, only this preparation has been searched in claim 1. The further reaction to compounds IX and IXa turns up in claim 8.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/36806

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2550111	A	13-05-1976	
		FR 2313060 A1	31-12-1976
		FR 2322600 A1	01-04-1977
		FR 2322601 A1	01-04-1977
		FR 2322602 A1	01-04-1977
		AR 208414 A1	27-12-1976
		AR 208800 A1	28-02-1977
		AT 343666 B	12-06-1978
		AT 401977 A	15-10-1977
		AT 343123 B	10-05-1978
		AT 848675 A	15-09-1977
		AU 503200 B2	30-08-1979
		AU 8633175 A	12-05-1977
		BE 835325 A1	06-05-1976
		CA 1057755 A1	03-07-1979
		CH 609057 A5	15-02-1979
		CS 7705983 A2	16-01-1984
		CS 231958 B2	16-01-1985
		CS 7507510 A2	16-01-1984
		CY 1045 A	01-08-1980
		DD 122684 A5	20-10-1976
		DE 2550111 A1	13-05-1976
		DK 499275 A ,B,	08-05-1976
		ES 442389 A1	16-04-1977
		ES 442390 A1	16-04-1977
		FI 753127 A ,B,	08-05-1976
		GB 1468497 A	30-03-1977
		HK 19380 A	18-04-1980
		HU 173108 B	28-02-1979
		IE 41928 B1	23-04-1980
		IL 48423 A	12-03-1979
		JP 1018394 C	28-10-1980
		JP 54098790 A	03-08-1979
		JP 55008508 B	04-03-1980
		JP 51070776 A	18-06-1976
		JP 54022996 B	10-08-1979
		LU 73738 A1	06-09-1976
		NL 7512732 A ,B,	11-05-1976
		NO 753713 A ,B,	10-05-1976
		OA 5162 A	31-01-1981
		PH 16806 A	01-03-1984
		PL 100434 B1	31-10-1978
		PL 101248 B1	30-12-1978
		SE 407063 B	12-03-1979
		SE 7512477 A	10-05-1976
		SU 673173 A3	05-07-1979
		SU 604496 A3	25-04-1978
		US 4220646 A	02-09-1980
		YU 192182 A1	21-01-1983
		YU 192282 A1	21-01-1983
		YU 281575 A1	21-01-1983